C.F.R. 1.129(a) or (b) for consideration of additional groups. However, by virtue of the priority date, this application has now been pending for eight years. Issuance of a restriction requirement at this time, after consideration on the merits of all pending claims and an appeal to the Board of Appeals and remand to the examiner, is blatantly unfair to the applicants, in view of the twenty year patent term form the date of first filing. It is totally inconsisent that, with no amendments having been made to the claims, consideration on the merits of all claims to the point of sending this application to the Board of Appeals, that the claims could now be drawn to separate inventions. Indeed, as the examiner is aware, all claims in issue are drawn to a single invention: the scavenger receptor protein and nucleic acid molecule encoding the scavenger receptor protein, which has been the subject of prosecution of this application and its parent, now allowed. The original restriction requirement in the parent application, U.S.S.N. 08/265,428, was made by this same examiner on August 28, 1995. This application was then filed with a preliminary amendment cancelling the claims prosecuted in the parent application. **No restriction requirement was ever made in this application until 2002. Indeed, the examiner has examined all pending claims on the merits in the outstanding office action.** Accordingly, rejoinder and continued consideration of all claims in this case is earnestly solicited. Should this restriction requirement be maintained, and any petition regarding the same be denied, then applicants elect the claims of group I.

Amendments to the Claims

Claims 14 and 15 have been rewritten in independent form.

Claims 11, 13, 44 and 48 have been amended to recite specific hybridization conditions.

Support for these limitations is found in the application at page 40, lines 24-31.

Claims 11, 44, 48 and 50 have also been amended to recite that binding specificity of the scavenger receptor is determined in the presence of 10% serum. As demonstrated by Figure 5, and discussed at page 29, lines 6-12, CD36 is distinguished from SR-BI binding at a minimum by virtue of the effect of LDL on the binding of acetylated LDL to the CD36 or SR-BI: binding of SR-BI to acetylated LDL is inhibited by LDL, binding of CD36 to acetylated LDL is not inhibited by LDL, under the conditions used in this assay. These conditions are recited at page 28, line 40, and at page 26, lines 12-15, and page 28, line 21-23, as in cell medium containing 10% serum. As demonstrated by the enclosed declaration under 37 C.F.R. 1.132 by Dr. Krieger, LDL inhibits the binding of SR-BI, but not CD36, to acetylated LDL in the presence of 5-10% serum, i.e., under physiological conditions.

Claim 49 has been amended to recite an administering step.

Rejections under 35 U.S.C. §112

Claims 11-13, 19-22, and 44-50 9-13, 15, 16, 17, 18, 19-22, and 44-50 were rejected under 35 U.S.C. §112 as non-enabled. These rejections are respectfully traversed.

The rejection states that the claims are not enabled for an isolated nucleic acid encoding a scavenger receptor protein lacking an amino acid sequence disclosed in SEQ ID NOS: 4, 6 and 8. The office action then refers to paragraph/section 5 of the office action mailed March 19, 1998. This rejects the claims on the basis that absent hybridization conditions, the claims are indefinite. This basis of the rejection should be overcome by insertion into the claims of defined hybridization conditions, as discussed above. It should be noted that SEQ ID No. 6 does not

encode SR-BI, but a totally distinct protein, SR-C, having a very distinct structure, amino acid sequence, and function, which is not being prosecuted in this application.

The second basis of the rejection is that the claims encompass proteins which would be so different from their natural forms that one would have no guidance as to how to make such molecules. This is also believed to have been overcome by the recitation of specific hybridization conditions, as well as the limitations regarding functional activity. In combination, one skilled in the art would have no difficulty making or using or identifying the claimed nucleotide molecules.

The claims are limited by the requirement that the cDNAs encoding the type B1 scavenger receptors must hybridize to the nucleic acid molecule of SEQ ID No. 2. Those of skill in the art know how to perform hybridization experiments that lead to specific gene recognition of homologues, and the present application **specifically describes** how to do this for a SR-B1 cDNA. For example, on page 18:line 27 to page 19:line 6 an explicit description of a hybridization procedure in which the isolated hamster SR-B1 cDNA is used to produce a 600 base probe (derived from a BamHI restriction digest of the DNA shown in Seq ID No. 3) which is used to probe different cell types from murine tissues and from 3T3 cells. The hybridization and washing conditions were done at 42° C and 50° C respectively using the well known conditions described by Charron et al. *Proc. Natl. Acad. Sci.* 86 2535-2539 (1989). Performing the hybridization analysis as described in the application clearly shows that a single predominant band of 2.4 kb was abundant in fat and present in moderate levels in lung and liver (page 31:line 11 to page 32:line 24). While the 600 base probe derived from the hamster scavenger receptor

type B1 cDNA hybridizes as single gene sequence in mouse, a probe from CD36 has a different hybridization pattern, indicating that the hybridization assay described is sufficient to differentiate between CD36 and applicants' nucleic acids encoding SR-B1 type proteins. This fact is significant since, as pointed out in the Office Action, other non-SR-BI genes are closely related in sequence to hamster and human SR-BI sequence (see Calvo et al.). This indicates that while CD36 and SR-B1 are related proteins (both members of the CD36 superfamily), they are not so related as to be considered homologues with each other. The hybridization methods clearly indicate that the scope of the claims is such that it would not include all members of the CD36 superfamily, only those that are in the class defined by the specification as type SR-B1. In other words, the hybridization conditions recited in the claims, results in the inclusion of SR-BI encoding sequences, but excludes sequences encoding non-SR-BI proteins (including other members of the CD36 superfamily). This is of course separate from the functional differences, as defined by the differences in binding activity, which further distinguishes the SR-BI from the CD36 proteins encoded by the nucleic acids, and therefore the nucleic acids *per se*.

The present rejection is based on the erroneous premise that the specification does not provide the guidance that is required to produce nucleic acids encoding proteins whose amino acid sequences have been substantially altered from natural forms in a predictable manner. The application provides numerous assays for determining the function of an SR-B1 receptor such as binding AcLDL. These assays allow those of skill in the art to determine which variants are functional and which are not functional. As described in the application and in the previously submitted Declaration under 37 C.F.R. 1.131, once one nucleic acid encoding type BI scavenger

receptor protein was obtained, it was routine to isolate a second molecule.

The standard for making a rejection based on 35 U.S.C. § 112, first paragraph, is articulated in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) (see also MPEP § 2164.01 and 2164.04). Initially, the Patent Office must accept the objective truth of statements made in the specification. If such statements are to be called into question, the Patent Office is burdened with providing evidence or convincing argument why those of skill in the art would doubt the statements. *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). This burden has not been met.

While 35 U.S.C. § 112 does not recite the words "undue experimentation", this is the standard that is to be applied when assessing whether an application enables the claimed invention. *In re Wands,* 858 F.2d 731, 737 8 USPQ2d 1400 (Fed. Cir. 1988). A determination of undue experimentation is a conclusion based on weighing many factors, not just a single factor. Many of these factors have been summarized in *In re Forman.* 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) and set forth in *In re Wands*. They are: (1) The quantity of experimentation necessary (time and expense); (2) The amount of direction or guidance presented; (3) The presence or absence of working examples of the invention; (4) The nature of the invention; (5) The state of the prior art; (6) The relative skill of those in the art; (7) The predictability or unpredictability of the art; and (8) The breadth of the claims.

First, its should be noted that the mere fact that claims encompass embodiments that are not explicitly described, nor exemplified, does not render the claims non-enabled. In fact, inclusion of some embodiments that are even inoperative would still not render the claims non-

enabled.

As articulated by this Board in *Ex parte Mark*, 12 U.S.P.Q.2d 1904 (Bd. Pat. App. & Int'f 1989), "When it is considered that the claims remaining on appeal all require that the mutein produced retain the biological activity of the native protein, we consider the disclosure of this application to be enabling . . . The fact that a given protein may not be amenable for use in the present invention in that the cystein residues are needed for the biological activity of the protein does not militate against a conclusion of enablement. One skilled in the art is clearly enabled to perform such work as needed to determine whether the cysteine residues of a give protein are needed for retention of biological activity." 12 U.S.P.Q.2d at 1906-1907.

As applied to the claims here, one skilled in the art can obtain starting material merely by reference to the application before him. He can readily compare the amino acid sequences for the hamster and mouse SR-BI proteins and determine which amino acids are conserved and which are not. He can enter the amino acid sequence into computer programs that are commercially available and look at the resulting structure, to determine which amino acids are located at critical regions. Even if an amino acid is changed, intentionally or accidentally or by nature, it would require no more than routine effort to screen for activity. The assays to screen for binding activity are detailed in the application and the expected ranges actually demonstrated. The minimal nature of the experimentation required to obtain these proteins is demonstrated by how applicants, with no knowledge of the existence of this protein nor its activity, were able to screen *an entire expression library* for activity, as they did to originally isolate the SR-BI from hamster cells. See in particular the studies reported at page 36, in which *3500 clones were*

screened initially for activity, then subdivided into 18 subpools of 350 clones which were transfected into cells and screened again. Applicants also demonstrated that they were able to obtain the mouse SR-BI DNA using the hamster DNA, with no more than routine effort. With the sequences of SR-BI proteins from two different species, and their activity profiles in hand, as well as the requirement that the nucleic acid hybridize to these known sequences, it would only require routine testing to determine which molecules are encompassed by the claims.

The CCPA first addressed the issue of protein variants in *In re Fisher*, 427 F.2d 833 (CCPA, 1970). Integral to this holding was the court's reliance on the knowledge of one of ordinary skill in the art, and the lack of a showing that one of ordinary skill in the art could obtain sequences other than 39 amino acids long. The court stated,

> The parent specification does not enable one skilled in the art to make or obtain ACTHs with other than 39 amino acids in the chain, and *there has been no showing that one of ordinary skill would have known how to make or obtain such other ACTHs without undue experimentation.* As for Applicant's conclusion that the 25th to 39th acids in the chain are unnecessary, *it is one thing to make such a statement when persons skilled in the art are able to make or obtain ACTH having other than 39 amino acids*; it is quite another thing when they are not able to do so.
>
> Id. at 836. (emphasis added).

It is clear that the court was placing great emphasis on what one of ordinary skill in the

art could have hoped to make or obtain. This decision was handed down in 1970, on an application filed November 29, 1960, claiming priority from an application filed June 9, 1954. The priority application was filed one year after Watson and Crick determined that the structure of DNA was a double helix (Watson and Crick *Nature* 171, 964-967 (1953)). It would still take seven years of research before scientists even knew that there was a triplet code between a DNA sequence and a protein sequence (Crick et al. *Nature* 192 1227-1232 (1961)). It is not reasonable to assume that a holding, based on an application filed in 1954, prior to the advent of biotechnology, is controlling on biotechnology itself. The court in *In re Fisher* very likely correctly held that "one could not make or obtain", without undue experimentation, a protein with less than 39 amino acids . . . *in 1954.* The court just as correctly noted though that if one of ordinary skill in the art could have made or obtained such a protein then the holding would have been very different. *Unlike this case*, applicants have demonstrated that one of ordinary skill in the art of cloning *in 1994* can obtain other nucleotide molecules encoding SR-BI with the requisite activity, without undue experimentation.

The court in *Amgen, inc. v. Chugai Pharmaceutical Co., LTD.*, 927 F.2d 1200 (Fed. Cir. 1991) relied heavily on the holding in *In re Fisher* to find a claim drawn to a large number of non-natural Erythropoietin (EPO) analogs invalid for failing to meet the requirements of 35 U.S.C. 112. The court focused on the number of possible analogs that were encompassed by the claim **and** on the uncertainty held by the applicant as to which analogs, already produced, possessed the activity. The trial court relied on expert testimony which provided that "Amgen is still unable to specify which analogs have the biological properties set forth in the claim." *Id.* at

1213. The Federal Circuit chose to focus on the making and using of the DNA sequences, which produce the protein which has the biological activity, rather than the biological activity itself. While the *Amgen* court spoke positively of *In re Angstadt*, 537 F.2d 498, 502, which held that it is not necessary that a patent applicant test all embodiments of his invention. just that he provide a sufficient disclosure to enable one skilled in the art to practice the full scope of the claims, they stated that for claims based on DNA sequences a sufficient disclosure meant, "disclosing how to make and use enough sequences to justify grant of the claims sought." *Id.* at 1213. The court went on to state, "what is relevant *depends on the facts*, and the facts here are that Amgen has not enabled *preparation of DNA sequences* sufficient to support its all-encompassing claims." *Id.* at 1213. (emphasis added). Again, as in *In re Fisher*, the focus is on what Applicants, or one of ordinary skill in the art could do. The court focused on whether the preparation of the DNA sequences, within the scope of the claims, could *be prepared.* The application at issue was filed on November 30, 1984 and claimed priority to an application filed on December 13, 1983. Therefore, the "facts" relevant to the "preparation of DNA sequences" in the courts mind were those that existed in 1983. This is almost four years prior to the advent of PCR. Chemical synthesis of DNA was still only able to routinely produce short oligonucleotides. In short, the two most important technological advances for the "preparation of DNA sequences" in a manner without "undue experimentation", PCR and highly efficient automated DNA synthesis, were still years away. A case decided based on the level of skill in the art *ten years earlier*, in a field changing almost hourly, cannot be used as a basis for a determination of what one skilled in the art would do as of 1994.

In *Hormone Research Foundation v. Genentech, Inc.* 904 F.2d 1558, 1568-69 (Fed. Cir. 1990). the court reversed a summary judgement for lack of enablement regarding claims directed to human growth hormone. The lower court had ruled that the alleged infringer had presented sufficient evidence indicating that the application was not enabled to merit summary judgement. (*Hormone Research Foundation v. Genentech, Inc.*, 708 F.Supp 1096 (N.D.Cal. 1988). The Federal Circuit remanded this issue for further adjudication because the lower court had failed to adequately address the analysis of *In re Hogan*, 559 F.2d 959 (CCPA 1977) and *United States Steel Corp. v. Phillips Petroleum Co.* 865 F.2d 1247 (Fed. Cir. 1989). In commenting on the relevance of these cases the *Hormone Research Foundation* court stated,

> It is unclear whether the high degree of potency and purity contemplated by the district court's analysis of enablement was influenced by the *potency and purity obtainable through recombinant DNA methodology*. Moreover, it is unclear from the record before us *whether that technology existed at the time the application was filed*. Further factual development as to the *state of the art at the date of the application* . . . is required for this court to review the enablement issues.
>
> *Id.* at 1568-1569. (emphasis added).

The meaning and intent of the court is clear: one must assess the question of enablement in the light of the knowledge of one of ordinary skill in the art *at the time the application is filed.* In this case, Applicants have demonstrated one can skill huge numbers of molecules rapidly and

without experimentation, and that it is possible to routinely obtain additional molecules encoding SR-BI merely by hybridization to one of the disclosed nucleotide molecules.

A central issue in the above cases is the level of predictability in the art. The question remains, however, as to what "unpredictability" means. For example, the court in *In re Vaeck* 947 F.2d 497 (Fed. Cir 1991) addressed the issue of unpredictability by stating, "we do *not* imply that patent applications in art areas currently denominated as unpredictable must never be allowed generic claims encompassing more than the particular species disclosed in their specification." *Id.* at 496. (emphasis contained in original). The court went on to state that "there must be sufficient disclosure . . . to teach those of ordinary skill how to make and how to use the invention . . ." *Id.* at 496. The question remains, what is a sufficient disclosure for an application that is in an "unpredictable" art? The clear answer given by the court was "the disclosure must adequately guide the art worker to determine, *without undue experimentation*, which species among all those encompassed by the claimed genus possess the disclosed utility. *Id.* at 496. (emphasis added). The court did **not** state, "without any experimentation," they stated "without undue experimentation". This means that a standard of "predictability" that excludes "all" experimentation is simply incorrect.

"Unpredictability" is often used as a sword by the PTO to slash the scope of a legitimate biotechnology claim. The sharpness and size of this sword, however, are unduly exaggerated because of the misapplication of what is and should be "predictable". In the area of functional variants, such as discussed in *In re Fisher* or *Amgen Inc., v. Chugai Pharmaceutical Co.*, the standard when assessing whether the specification enables one of ordinary skill in the art to make

and use the claimed variants is whether it would require "undue experimentation" to determine which variants are functional. In the language of *In re Vaeck*, "the disclosure must adequately guide the art worker to determine, *without undue experimentation*, which species among all those encompassed by the claimed genus possess the disclosed utility. *Id.* at 496.

The priority date for the application is June 23, 1994. By this time technologies such as PCR were highly developed and were routinely utilized to "prepare" DNA molecules which encoded for variants of known protein sequences. The importance of utilizing PCR cannot be overestimated with respect to the manipulation of DNA molecules, and specifically the insertion, deletion or substitution of DNA sequences which lead to changes in the amino acid sequence of a protein. The specification contains ample description of recombinant DNA methods that enable one of ordinary skill in the art to make SR-B1 receptors with varied amino acids. For example, on page 51 the subsection entitled "Preparation of Receptor Protein Fragments" describes numerous methods including cleaving the protein with various proteases, expression of the altered protein from a recombinant DNA molecule, and even chemical synthesis of the desired protein fragment. On page 52:lines 14-18 the specification states, "These methods can be used to synthesize peptides having identical sequence to the receptor proteins described herein, or substitutions or additions of amino acids, which can be screened for activity."

The "preparation of the DNA molecules" encoding the variants of the sequences disclosed in SEQ ID NOs. 4 and 8 are fully enabled by the specification. Likewise, the assays to determine those variants that have the desired activity are readily described. The claims require that the nucleic acids encoding the SR-B1 receptor are capable of hybridizing with either SEQ

ID. Nos. 3 or 7, and that it selectively binds to low density lipoprotein and modified lipoprotein. Assays for determining whether the modified DNA molecules hybridize to SEQ ID Nos. 3 or 7 are described at least from page 18:line 27 to page 19:line 6. As is indicated in these pages these methods were published in 1992, approximately three years before the priority date of the application. Clearly one of ordinary skill in the art would be able to practice techniques that were nearly three years old. In addition the application describes a number of assays that indicate whether a candidate SR-B1 protein binds low density lipoprotein and modified lipoprotein as required by the claims. For example, on page 19 there is a subsection entitled "HDL Binding Studies" and following this section is the description of "Phospholipid Binding and Competition Assays." On page 21 there is yet another section entitled "Ligand Binding Assays" that discloses methods for determining if various low density lipoproteins and modified lipoproteins bind cells containing candidate SR-B1 receptors.

Notwithstanding the above, the specification provides working examples of SR-B1 proteins having different amino acid sequences that meet all of the requirements of the claims, the hamster homologue of SR-B1 and the murine homologue of SR-B1. While the applicant has not actually made "synthetic" variants of the SR-B1 protein, nature has provided the necessary evidence that there are protein variants of the hamster SR-B1 that exist which meet the limitations of the claims. There are numerous positions in the amino acid sequence of the murine homologue to the hamster SR-B1 that are "variant" from the hamster SR-B1 sequence. The application teaches one how to make the protein variants, the application teaches one how to test the protein variants for activity, and the application teaches one that not every amino acid is

required for function as required by the claims. The latter demonstration is what a working example can provide for an application, and this demonstration is provided by the fact that multiple homologues are disclosed.

The prior art made of record, while not explicitly required by the *Wands* factors, clearly supports the enablement of protein variants. For example, Cullen et al, "Use of Eukaryotic Expression Technology in the Functional Analysis of Cloned Genes," *Methods in Enz.* 152:684-704 (1987) describes numerous methods for producing eukaryotic expression vectors, such as those used in the present specification, to test specific DNA sequences for activity. Methods for domain swapping and protein mutagenesis were readily known to those of ordinary skill in the art and this is exemplified by Daugherty, et al., "Polymerase chain reaction facilitates the cloning, CDR-grafting and rapid expression of a murine monoclonal antibody directed against the CD18 component of leukocyte integrins," *Nucl. Acids Res.* 19:2471-2476 (1991).and Itakura et al., "Synthesis and use of synthetic oligonucleotides," *Ann. Rev. Biochem.* 53:323-356 (1984). Daugherty et al. describes methods for using the Polymerase Chain Reaction (PCR) to swap functional domains of a specific antibody between the murine and human homologues. Itakura et al. actually discusses site mutagenesis prior to PCR and describes this technology, in 1984, by saying "The once seemingly obvious limitations of this technique [referring to site directed mutagenesis] –availability of synthetic DNA and a knowledge of the nucleotide sequence of the target region—are no longer major factors." *Id.* at 343-344. Thus, in 1984, 10 years before the priority date of this application, the opinion of those of ordinary skill in the art was that the factors which arguably caused undue experimentation to make protein variants prior to 1984, "are no

longer major factors" after 1984.

Claim 19 has also been rejected under 35 U.S.C. §112, first paragraph, on the basis that the applicant did not have possession of the invention as of the date of filing. This rejection is respectfully traversed.

The facts in this case are that the applicants obtained the sequences encoding hamster SR-BI and used the hamster sequence to obtain the mouse sequence, with standard hybridization techniques, from a standard expression library. The high degree of homology between hamster, murine and human SR-BI are proof that one could have similarly obtained the human SR-BI without undue experimentation. However, because applicants knew this was routine, they focused their efforts on expressing the protein and characterizing its activity, which could not have been predicted from the nucleotide or protein sequence. This work, showing the structure and function of the SR-BI protein and nucleotide sequence in general, was completed prior to September 5, 1993. Shortly thereafter, applicants screened the data base and found that a sequence encoding a protein whose function was not known, was in fact the sequence encoding human SR-BI. It is particularly significant that Calvo did not know the function of the protein, only the sequence. This sequence was obtained by searching a data base using the sequence provided by applicants, as taught by applicants.

The standard for enablement under 35 U.S.C. §112, is discussed above. It is premised on whether or not one of skill in the art could make and use that which is defined by the claims as of the date of filing of this application. There can be no question that applicants had possession of the sequence encoding human SR-BI as of the date of filing since they had obtained the full

sequence encoding two different species of SR-BI, hamster and mouse, they had identified conditions wherein hybridization specifically to SR-BI of different species occurred, they had been able to search available data bases for sequences encoding SR-BI or other species to determine if they also encoded SR-BI or a different protein. Indeed, this comparison led to identification of CD36, which was homologous by data base comparison, and then distinguished by functional activity (and by the low degree of homology as compared to the homology between SR-BI of different species). Based on the high degree of homology, as described in the declaration under 1.131 that says there there is 80% identify between hamster and human SR-BI encoding sequence and 81% identifity between hamster and human SR-BI protein sequence, one skilled in the art had no trouble obtaining the sequence encoding the human SR-BI. This is further evidenced since the sequence was readily obtained using the hamster SR-BI sequence from a review of data bases. See also the discussion on page 27, line 34, to page 28, line 5, showing that in the case of the closely related CD36 protein, the homology between CD36 of various species of origin is all within 1%, evidencing the high degree of predictability between proteins and therefore that one skilled in the art could obtain the sequence for human SR-BI with only routine experimentation. The specification describes methods of obtaining the human homologue of SR-B1 on page 38, lines 12-27 using the sequences disclosed in the specification. These methods fully enable one of skill in the art to obtain the human homologue of SR-B1.

Furthermore, the issue of description is adequately met simply by constructively reducing the material to practice (*Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991)). The Court in *Vas-Cath Inc. v. Mahurkar* stated, "Whether the disclosure of the

application relied upon reasonably conveys to the skilled artisan that the inventor had possession at the that time [i.e., when the application was filed] of the later claimed subject matter." As long as the subject matter was described in the specification as it was claimed, the description requirement is met. Applying this standard, the human homologue as claimed in claim 19 clearly meets the description requirement.

In so far as the Examiner is relying on *Regents of the University of California v. Eli Lilly and Company*, 43 USPQ2d. 1398 (CAFC 1997) as the basis for this rejection, Applicants note that *Regents of U.C.* is not applicable since the claims and underlying specification here are not analogous to the facts there. The Court in *Regents of U.C.* relied on the fact that the description of example 6 in the patent at issue prophetically described obtaining a cDNA sequence from the **protein** sequence of the human protein. This is completely different then the situation here, where the specification relies on the use of the homologous cDNA as a probe, not a degenerate sequence obtained by reverse translation of a protein sequence. This difference is absolutely critical because the Court in *Regents of U.C.* relied on their own precedence of *In re Deuel* 51 F.3d 1552, 1558, 34 USPQ2d 1210, 1215 (1995). The Court stated, "A prior art disclosure of the **amino acid sequence** of a protein does not necessarily render particular DNA molecules encoding the protein obvious because the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences encoding for the protein." In relying on the relationship of amino acid sequence to nucleic acid sequence, *Regents of U.C.* is limited to protein-to-DNA situations. It should be noted that the court in *Regents of U.C.* did not specifically address (and thus, did not overrule) the standard that has been accepted for the

description requirement for the last 125 years, most recently explicated in *Vas-Cath Inc. v Mahurkar*.

Claim 49 has been amended to recite "administering a compound" to inhibit binding.

Claim 44 and claims dependent thereon have been amended to recite that the assay reagents include SR-BI, low density lipoprotein or acetylated low density lipoprotein, and means to determine if the low density lipoprotein or acetylated low density lipoprotein is bound by the SR-BI.

Claims 11 to 15, 19 to 22, and 44-50 were rejected on the basis that the term scavenger receptor protein is indefinite. This is believed to be mooted by the amendment defining the hybridization conditions present in all claims.

Claim 14 has been amended to delete the phrase "or degenerate variant thereof" although it is to be noted that the examiner had stated this claim was allowable.

Claims 21 and 22 have been rephrased as suggested by the examiner.

Claim 46 does not contain the objected to language "naturally occurring or synthetic".

Rejections under 35 U.S.C. §102(a) and 103

Claims 11, 19 and 20 were rejected as disclosed by Calvo, et al. J. Biol. Chem. 268(25), 18929-18935 (September 5, 1993). Claims 21 and 22 were rejected under 35 U.S.C. §103 as obvious over Calvo, et al.. These rejections are respectfully traversed.

For a rejection of claims to be properly founded under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 US 947

(1987); *Scripps Clinic & Research Found v Genentech Inc*, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 18 USPQ2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . *There must be no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps, Id.*:

> [A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

For a prior art reference to anticipate a claim, it must enable a person skilled in the art to practice the invention. The Federal Circuit held that "a §102(b) reference must sufficiently describe the claimed invention to have placed the public in possession of it. . . [E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling." *Paperless Accounting Inc v Bay Area Rapid Transit Sys.*, 231 USPQ 649, 653

(Fed. Cir. 1986) (citations omitted).

37 C.F.R. § 1.131 states, in pertinent part,

> (a)(1) When any claim of an application . . . is rejected under 35 U.S.C. 102 (a) or (e), or 35 U.S.C. 103 based on . . . reference to . . . a printed publication, the inventor of the subject matter of the rejected claim . . . may submit an appropriate oath or declaration to overcome the . . . publication. The oath or declaration must include facts showing a completion of the invention in this country or in a NAFTA or WTO member country before . . . the date of the printed publication.
>
> * * *
>
> (b) The showing of facts shall be such, in character and weight, as to establish reduction to practice prior to the effective date of the reference, or conception of the invention prior to the effective date of the reference coupled with due diligence from prior to said date to a subsequent reduction to practice . . . .

The Applicant need only provide evidence that reasonably gives rise to an inference that the invention was completed before the reference date, in order to constitute a *prima facie* showing. No corroboration is required since the application process is *ex parte*. A Rule 131 affidavit is sufficient when it demonstrates that the Applicant has prior "possession" of that part of the invention disclosed by the reference, as is the case when a reference discloses a species

falling within a claim to its genus. *See* Donald S. Chisum, **Patents** § 3.08[1][b] (Matthew Bender & Co. 1996). Possession in this context is shown by demonstrating conception, reduction to practice, and diligence--each as normally required in determining the date of invention. *See In re Mulder*, 716 F.2d 1542 (Fed. Cir. 1983).

In *In re Stempel*, 241 F.2d 755 (C.C.P.A. 1957), the court held that Applicant's affidavit under Rule 131 was not required to show priority with respect to the claimed genus, but only to the species disclosed by the cited reference, in order to remove that reference as prior art. The claims, both genus and species were drawn to chemical compounds. *Stempel* overcame the anticipation rejection by showing reduction to practice, prior to the effective date of the reference, of a species of the invention within the generic claims.

In *In re Tanczyn,* 347 F.2d 830 (C.C.P.A. 1965), the court qualified *In re Stempel*, stating that the *Stempel* doctrine did not apply to *partial* possession of the invention, as distinguished from *total* possession of a species within a genus claim. The *Tanczyn* application "did not involve a genus-species relationship." Id. at 833.

In *In re Clarke,* 356 F.2d 987 (C.C.P.A. 1966), the court extended the *Stempel* doctrine to the situation at issue in this application, that is where the Applicant's Rule 131 affidavit shows possession that is *not* of the entire invention nor of the part of the invention disclosed by the reference. The *Clarke* court held that the affidavit is sufficient to remove a reference where the Applicant demonstrates possession of such "invention" as to make the entire claimed invention or the reference part obvious to one of ordinary skill in the art. The court stated,

"[i]n an appropriate case an Applicant should not be

> prevented from obtaining a patent to an invention where a compound described in a reference would have been obvious to one of ordinary skill in the art in view of what the affiant proves was completed with respect to the invention prior to the effective date of the reference. . . . Thus, we think that in an appropriate case a single species could be sufficient to antedate indirectly a different species of a reference.".

The CCPA also has phrased the rule, "[w]hen that species of the generic invention which has been completed prior to the effective date of the reference would make obvious to one of ordinary skill in the art the species disclosed in the reference, the reference may be said to have been 'indirectly antedated.'" *In re Schaub*, 537 F.2d 509, 512 (C.C.P.A. 1976) (quoting *In re Ranier*, 390 F.2d 771, 773-74 (C.C.P.A. 1968)). The *Schaub* court stated that "[a]ppellants have made a *prima facie* case that the compound of the reference is obvious from the compounds which they have made prior to the date of the reference. Applicants' compound III is the next higher homolog of the reference compound II, . . ." Id. at 512-13.

There is little, if any, Federal Circuit case law on point. However, the rule established in *In re Clarke* apparently remains valid, as one somewhat recent, "unpublished" (i.e. not citable as precedent) case seems to indicate. In *In re Rozmus*, 928 F.2d 412, 1991 WL 17232 (Fed. Cir.), the court stated that "[a]lthough Rozmus' [Rule 131] declaration showed reduction to practice of only a species of the generic invention, that alone is not fatal to his claim. **A declaration proving a species is also sufficient to show possession of 'variations and adaptations which**

would, at the same time, be obvious to one skilled in the art.'" (quoting *In re Spiller*, 500 F.2d 1170, 1178 n.5 (CCPA 1974)) (emphasis added).

Other cases discussing priority but which do not involve Rule 131 have stated, "[p]riority as to a genus may . . . be shown by prior invention of a single species, but the genus will not be patentable to an Applicant unless he has generic support therefor." *In re Zletz*, 893 F.2d 319, 323 (Fed. Cir. 1989); *see also Hoffman v. Schoenwald* 15 U.S.P.Q.2d 1512, 1514 (Bd. Pat. App. & Int'f 1990) ("Conception of a species within the genus constitutes conception of the genus for priority of invention purposes.").

Calvo, et al. reported isolation of a cDNA encoding a member of the CD36 superfamily. The protein was not physically isolated nor was the cloned DNA expressed, much less expressed on the surface of cells and shown to be functional, although a small piece non-functional portion (the carboxyl terminal region including residues 365-409) was expressed as a chimeric protein (page 18930). The function of the protein was not known, although its resemblance to CD36/LimpII was recognized based on the predicted similarities in structure and the authors speculated that "on the basis of its structural homology to CD36 that CLA-1 could act as a receptor for extracellular products" (page 18934). As demonstrated by Applicants in the specification and in more detail below, CD36 and SR-BI are *not* the same proteins nor do they have the same binding activity.

Calvo, et al., did not express the full length, functionally active protein, and therefore could not determine the utility of the protein. As the Board of Appeals stated in their decision on page 13, "if the prior art does not teach any specific or significant utility for the disclosed

compounds, then the prior art is not sufficient to render structurally similar claims prima facie obvious".

A Declaration under 37 C.F.R. §1.131, submitted in the parent application, U.S. Serial No. 08/265,428, filed June 23, 1994, which demonstrates that a cDNA and encoded protein defined by the claims in issue was conceived and reduced to practice prior to the publication of Calvo, et al. was submitted with the Response to An Office Action, mailed on December 29, 1997. This Declaration proves that Applicants cloned the gene, they expressed the protein, and they characterized the protein and showed its function, **prior to** Calvo's publication date.

The Examiner has stated that the Declaration under Rule 1.131 does not "demonstrate that the Applicant was in possession of the any information regarding a CLA-1 protein or CLA-1 gene from any animal other than hamster prior to the publication of Calvo et al." Applicants respectfully point out that this is not in fact true. Submitted with the Declaration is a printout obtained from the search of six databases (PDP, Swissprot, PIR, SPupdate, Genpept, GPupdate). This printout indicates that the Rat LimpII gene and the CD36 gene were among the genes with the highest homology to SR-B1. While these genes have been shown to be members of a different families within the superfamily of CD36 scavenger receptors than the SR-B1 proteins of the present application, for one of ordinary skill in the art they presented a nexus between the species described in the Declaration of Krieger and Acton and the genus which would include the CLA-1 gene described in Calvo et al. The validity of these assertions is evidenced by the fact that the CLA-1 gene was isolated using primers derived from CD-36 and LIMP II, related but non-homologous proteins. Surely, the possession of the homolog of the CLA-1 protein, with

the information that it fell within the CD-36 superfamily, is more information than Calvo et al. had when they cloned the CLA-1 gene, but not the homolog, from rat. The Applicants clearly were in possession of the genus of SR-B1 proteins and nucleic acid molecules that encode these proteins prior to the publication of Calvo.

Furthermore, the Examiner has stated, "There is no evidence in this Declaration that a nucleic acid probe encoding all or part of hamster CLA-1 was capable of hybridizing to mouse DNA or that a DNA encoding a murine cDNA had been isolated." This statement is incorrect. The latter is obviously wrong - SEQ ID NO. 7 *is* the nucleic acid sequence encoding the murine SR-BI. Moreover, the specification provides exactly the type of evidence the Examiner is looking for. For example, on page 18, line 27 to page 19, line 6 there is an explicit description of a hybridization procedure in which a 600 base probe of derived from the hamster SR-B1 cDNA is used to probe different cell types from murine tissues and from 3T3 cells. The results from these experiments clearly shows that a single predominant band of 2.4 kb was abundant in fat and present in moderate levels in lung and liver (page 31, line 11 to page 32, line 24). This data not only directly indicates an interspecies hybridization abundance, it indicates that this relationship is specific and successful because it recognizes the murine homologue in only those tissues that express it. The genus of the claims is described as cDNAs encoding Scavenger Receptor Protein type B1, having specific functional properties, and includes the SR-B1 cDNA of the present application and the CLA-1 cDNA of Calvo et al. This genus is a subgenus of the genus of CD36 superfamily of scavenger receptor proteins which includes CD36 and LimpII.

To one of ordinary skill in the art there would have been more than sufficient motivation

given the sequence homology data presented in the Declaration to utilize the information obtained from the novel hamster SR-B1 to isolate the human homologue based on the information provided in the specification and the general knowledge known in the art.

Claim 11 and 20 are not specific to human SR-BI – they claim any nucleotide molecule encoding SR-BI, as defined by specific hybridization conditions and encoding a protein having a defined functional activity. The sequences defined in claims 11 and 20 are novel because the Krieger and Acton Rule 1.131 Declarations show that applicants had obtained, analyzed and expressed an isolated nucleotide molecule encoding SR-BI which hybridized to SEQ ID NOs:3 and 7, and encoded a protein having the define function. The entire sequence of the hamster and murine clones was not obtained until after Calvo was published, but the entire sequence was not required in order to meet the claimed limitations of claims 11 and 20, *since the claimed nucleotide molecule was already in hand, analyzed, made and used, in compliance with 35 U.S.C. §112. The requirements of claim 11 are not that the molecule have the specific sequence of SEQ ID NO3 or 7, but that it hybridize to SEQ ID NO:3, which it clearly did.*

Claim 19 is novel and separately patentable over Calvo et al. because as discussed above the Rule 1.131 Declaration presented by Drs. Krieger and Acton indicates that the Applicants were in possession of the claimed subject matter prior to the publication of Calvo et al. Furthermore, as discussed above with respect to the case law on this issue, since the human homolog was unquestionably obvious over the isolated nucleotide molecules obtained by and expressed by applicants, the 1.131 Declaration is sufficient to antedate a "different species" within the genus, thereby removing Calvo as prior art against the claims.

The law is quite clear that, for the Patent Office to establish a *prima facie* case of obviousness of claimed subject matter, the prior art references relied upon must provide *both* a suggestion to make the claimed invention and a reasonable expectation of success. It is also clear that the whole field of the invention must be considered, including those publications which teach away from the claimed invention. Particularly relevant to the matters under consideration here are the decisions of the Court of Appeals for the Federal Circuit in *In re Dow Chemical*, 5 USPQ2d 1529 (1988) and *In re Vaeck*, 20 USPQ2d 1438 (1991). The *Dow* Court noted that:

The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art.... Both the suggestion and expectation of success must be founded in the prior art, not in the applicant's disclosure.

The decision by the Board of Appeals at page 13 is further relevant to this rejection. Calvo, et al., did not know what their nucleotide molecule encoded, other than a protein with some similarity to CD36. They could not tell someone how to use it, or what it was for, since they did not know. One skilled in the art is not led to other members of a species when one does not know what one has. Moreover, as discussed above, the Krieger and Acton Declaration clearly shows that the Applicants were in possession of the cDNA and expressed protein prior to the date of Calvo et al. Therefore, Calvo et al. is antedated and not effective 35 U.S.C. § 103 art.

However, it cannot make obvious the genus where there was no expression of a protein, nor recognition of its properties. Among the reasons that the Examiner has argued that it would be obvious to go from the Human CLA-1 gene described by Calvo et al. to the hamster

homologue are: (1) CLA is described as being structurally analogous to LIMPII: (2) amino acid sequence were highly conserved between human and rat LIMPII; (3) the genes had sufficient similarity to permit the isolation of LIMPII; (4) an artisan would have concluded that any mammalian protein encoding CLA-1 would have been readily isolated by probing a DNA library, since the hamster, as well as rat, was routinely employed as a laboratory model for determining the physiological significance of proteins of human origin since the scope of human experimentation is obviously limited, (5) and there was knowledge that there was homology between humans and rodents at the time. [Applicants note, in passing, that each and every one of these reasons, relied upon by the Examiner to support the "*prima facie*" case of obviousness to clone the hamster SR-B1 protein from the sequence information of the human CLA-1 protein were presented in the specification and Declaration in the present application, and one must assume that the Examiner may have used hindsight based on this Declaration to identify reasons why one would go from Calvo to what is claimed, rather than from what Applicants have demonstrated they conceived and reduced to practice, prior to Calvo, to arrive at what Calvo disclosed.]

Applicants do not understand how, in the light of the Declaration submitted, the Examiner can maintain that it was *prima facie* obvious to clone the hamster homologue of the human CLA-1 when Applicants have demonstrated possession of the hamster gene before the date of the publication of the human homologue CLA-1. Furthermore, in light of the Examiner's rejection of claim 19 under 35 U.S.C § 112 for an inadequate description of the human homologue of SR-B1, which implicitly relies on *Regents of the University of California v. Eli*

Lilly and Company, 43 USPQ2d. 1398 (CAFC 1997), it is inconsistent to maintain a rejection which is contrary to the Examiner's only interpretation and reliance on case law. Applicants have distinguished themselves not only from *Regents of the University of California v. Eli Lilly and Company* (as discussed above), but also assert that in the light of the Declaration and the evidence provided in the specification, it would have been *prima facie* obvious to clone the human homologue of SR-B1 from what Applicants had well prior to the publication by Calvo!

Applicants have demonstrated that they cloned and expressed the hamster gene encoding the claimed SR-BI proteins, and that the gene hybridizes to the murine gene, prior to publication by Calvo et al. Accordingly, Applicants conceived of and reduced to practice the claimed invention prior to Calvo et al. Therefore, the Declaration under 37 C.F.R. §1.131 should conclusively remove Calvo et al. as a reference, and the claims found patentable to Applicants.

Claims 21 and 22 are not made obvious by Calvo et al. and are separately patentable. Calvo et al. does not disclose the expression of the molecules of claim 11 in a host cell nor preparation of a vector including the molecules of claim 11. Calvo shows a vector including only a very small piece of the Cla-1 cDNA, which was expressed as a chimera with a completely unrelated protein. The Examiner has failed to meet his burden of extablishing a *prima facie* case of obviousness because there has been no showing that Calvo et al. ever expressed active, functional protein, knew what function to look for, or how to look for related proteins. In addition, there is nothing in Calvo et al. that would lead one to express the molecules of claim 11. Therefore, claims 21 and 22 are patentable over Calvo et al.

In summary, claims 11, 19, and 20 are not disclosed by, nor claims 21 and 22 obvious

over Calvo, et al., since Calvo, et al. reported only the isolation of a cDNA encoding a member of the CD36 family. The protein was not physically isolated nor was the cloned DNA expressed on the surface of cells and shown to be functional, although a small piece (the carboxyl terminal region including residues 365-409) was expressed as a chimeric protein (page 18930). The function of the protein was not known, although its resemblance to CD36 was recognized based on the predicted similarities in structure and the authors speculated that "on the basis of its structural homology to CD36 that CLA-1 could act as a receptor for extracellular products" (page 18934).

It is well established that reduction to practice does not occur merely upon reporting of the existance of a material in the literature; constructive reduction to practice can only occur upon filing of a patent application.To prove a reduction to practice, an applicant must show that "the embodiment relied upon as evidence of priority actually worked for its intended purpose." *Holmwood v. Sugavanam* 948 F.2d 1236, 1238, 20 U.S.P.Q.2d (BNA) 1712 (Fed. Cir. 1991), *quoting Newkirk v. Lulejian*, 825 F.2d 1581, 1582, 3 U.S.P.Q.2d (BNA) 1793, 1794 (Fed. Cir. 1987). There can also be no constructive reduction to practice, since it is well established that constructive reduction to practice only occurs upon filing of a patent application. *Popeil Bros., Inc. v. Schick Electric, Inc.*, 356 F. Supp. 240, 244, 176 U.S.P.Q. (BNA) 101 (N.D. Ill 1972), *aff'd*, 181 U.S.P.Q. (BNA) 482 (7th Cir. 1974).

Accordingly, at most Calvo, et al. discloses a DNA encoding a CD36 protein of human origin, with unknown function. Therefore Calvo, et al., is not available under 35 U.S.C. 102 or 103, regardless of whether or not not applicants have demonstrated conception and reduction to

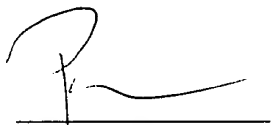
practice prior to the publication of Calvo, et al.

Claims 11 and 19-22 were also rejected under 35 U.S.C. §102(b) as disclosed by Oquendo, et al., Cell 58:95-101 (1989). This rejection is respectfully traversed if applied to the amended claims.

Oquendo, et al., discloses a nucleotide molecule encoding CD36. SR-BI differs both structurally and functionally from CD36, and is encoded by a nucleotide molecule which does not hybridize to the nucleotide molecule encoding CD36 under the claimed conditions. The claims have been amended to recite the differences in binding activity of the two proteins, as further evidenced not only by Figure 5 in the application but also the enclosed Declaration under 37 C.F.R. §1.131. Accordingly, the claims are not anticipated by Oquendo, et al.

Allowance of all claims 1-15, 19-22, and 44-50, as amended, is earnestly solicited.

Respectfully submitted,



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CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner of Patents, Washington, D.C. 20231.

Date: July 3, 2002

Patrea L. Pabst

APPENDIX: Marked up Copy of Claims as pending upon entry of this amendment

11. (twice amended) An isolated nucleic acid molecule encoding a scavenger receptor protein type BI which selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein in cell medium containing 10% serum, which hybridizes to SEQ ID Nos. 3 and 7 under moderately stringent hybridization conditions at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA.

12. (amended) The molecule of claim 11 expressed in cells selected from the group consisting of adipocytes, lung cells and liver cells.

13. (twice amended) The molecule of claim 11 hybridizing under stringent hybridization conditions at a temperature greater than 25°C below the melting temperature of a perfectly base-paired double-stranded DNA to a molecule with Sequence ID No. 3.

14. (twice amended) [The] An isolated nucleic acid molecule [of claim 13] encoding a scavenger receptor protein having the sequence of Sequence ID No. 3 [or a degenerate variant thereof].

15. (twice amended) [The] An isolated nucleic acid molecule [of claim 11] encoding a protein with the amino acid sequence shown in Sequence ID No. 4.

19. (amended) The molecule of claim 11 which encodes a human scavenger receptor.

20. (amended) The molecule of claim 11 labeled with a detectable label.

21. (three times amended) [A nucleic acid molecule] An expression vector comprising the molecule of claim 11 encoding the scavenger receptor protein [and an expression vector].

22. (three times amended) A [composition comprising a] host cell [suitable for expression of a scavenger receptor wherein the host cell comprises] comprising the nucleic acid molecule of claim [21] 11.

44. (twice amended) A method for screening for a compound which alters the binding of scavenger receptor protein type BI, which is encoded by a nucleotide molecule hybridizing to SEQ ID Nos. 3 and 7 under moderately stringent hybridization conditions at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA and which selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein in cell medium containing 10% serum, comprising

providing reagents for use in an assay for binding of low density lipoprotein or modified low density lipoprotein to the scavenger receptor protein the reagents comprising SR-BI, low density lipoprotein or modified low density lipoprotein, and means for determining if the low density lipoprotein or modified low density lipoprotein is bound to the scavenger receptor protein,

adding the compound to be tested to the assay, and

determining if the amount of modified low density lipoprotein or low density lipoprotein which is bound to the scavenger receptor protein is altered as compared to binding in the absence of the compound to be tested.

45. (amended) The method of claim 44 wherein the assay includes a cell expressing the scavenger receptor protein and the compound is a nucleic acid molecule which alters expression

of the scavenger receptor protein.

46. (amended) The method of claim 44 wherein the compound is selected from a library of compounds which are randomly tested for alteration of binding.

47. (amended) The method of claim 44 wherein the compound competitively inhibits binding of low density lipoprotein or modified lipoprotein having the characteristics of acetylated low density lipoprotein to the scavenger receptor protein.

48. (twice amended) A method for removing low density lipoprotein from patient blood comprising reacting the blood with immobilized scavenger receptor protein type B, wherein the scavenger receptor protein type BI is encoded by a nucleotide molecule hybridizing to SEQ ID Nos. 3 and 7 under moderately stringent hybridization conditions at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA and selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein in cell medium containing 10% serum, under conditions wherein the low density lipoprotein is bound to the scavenger receptor.

49. (twice amended) A method for inhibiting uptake of lipoprotein or lipids by adipocytes comprising

administering a compound selectively inhibiting binding of lipoprotein to the scavenger receptor protein type BI, wherein the scavenger receptor protein type BI is encoded by a nucleotide molecule hybridizing to SEQ ID Nos. 3 and 7 and selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein, under conditions wherein the low density lipoprotein is bound to the scavenger

receptor.

50. (amended) A method for screening patients for abnormal scavenger receptor protein activity or function comprising

determining the presence of scavenger receptor protein type BI, wherein the scavenger receptor protein type BI is encoded by a nucleotide molecule hybridizing to SEQ ID Nos. 3 and 7 under moderately stringent hybridization conditions at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA and selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein, and

determining if the quantity present or the function of the receptor is equivalent to that present in normal cells.